REMARKS

Claims 1-42 are pending.

Introduction

In addition to chitosan's lack of toxicity and allergenicity, and because of its biocompatibility, biodegradability and bioactivity, chitosan is an attractive material for diverse applications in pharmacy and medicine, where it is used for systemic and local delivery of drugs and vaccines.

Until the present application, available methods of chitosan gel formation did not allow for controlled structure assembly without the use of additional materials that could modify cross-links or cause a secondary acetylation. Durable chitosan salt gels that could be diluted with water or acid were previously impossible to make, as well as methods to produce thermally stable gels. The present application remedies these deficiencies.

Rejections under 35 U.S.C. § 103

The Office has rejected claims 1-9 under 35 U.S.C. § 103(a) as being unpatentable over (Goosen *et al.*, 1990) in view of (Struszczyk and Kivekas, 1996). Applicants respectfully traverse the rejection. The teachings of Goosen *et al.* (1990) combined with Struszczyk *et al.* (1996) fail to teach each and every limitation of the claims of the rejected claims. Furthermore, one of skill in the art would have no motivation to combine or to modify the cited references to arrive at the claimed invention because the references deal with different chitosan compositions. Neither reference discloses a chitosan-calcium (II) complex wherein the calcium (II) ion content is $\geq$ 0.1 wt% relative to chitosan. Furthermore, the chitosan of the references is not formed of a gel of chitosan salt to which calcium (II) ions are bound.

"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or [by] . . . .one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations" (*MPEP* 706.02(j)). This final point should not be based on the application's disclosure (*MPEP* 706.02(j)).

Goosen *et al.* (1990) teach chitosan-alginate gel matrices (not chitosan-calcium (II) complexes) that are useful in the culturing of cells, such as hybridoma cells, in enclosed capsules. The Office has cited Goosen *et al.* (1990) for the characteristics of the Goosen *et al.* chitosan-alginate gel matrix, wherein the chitosan has a molecular weight greater than 10 kD and a pH of 6.5. Goosen *et al.* teach that chitosan can be used to replace, or used in addition to, poly-L-lysine (PLL) with the objective of reducing the viscosity of the intra-capsular alginate solution after capsule formation and in forming a semi-permeable capsule membrane (Example 2 in column 6). The According to the Office, Goosen *et al.* (1996) also do not disclose the chitosan characteristics of polydispersity, deacetylation and water retention value. Not noted by the Office, however, is that Goosen *et al.* (1996) do not disclose that the chitosan in the chitosan-alginate gel matrix is a chitosan-calcium (II) complex wherein the calcium (II) ion content is $\geq$ 0.1 wt% relative to chitosan. Furthermore, the chitosan is not formed of a gel of chitosan salt to which calcium (II) ions are bound.

Struszczyk *et al.* (1996) teach the use of microcrystalline chitosan to encrust seeds such that they are protected from disease and pests until sown. The Office has cited Struszczyk *et al.* (1996) because of the characteristic of microcrystalline chitosan having an average molecular weight of 7800, deacetylation degree of 72%, and water retention value of 1240%. However, the Office did not note, that as in Goosen *et al.* (1990), the disclosed chitosan in Struszczyk *et al.* (1996) is not defined by calcium content, such that calcium (II) ion content is $\geq$ 0.1 wt% relative to chitosan. Furthermore, the chitosan disclosed in Struszczyk *et al.* (1996) is microcrystalline, not as chitosan-calcium complexes comprised of calcium (II) ions bound to a gel of a chitosan salt.

Because neither reference discloses a chitosan-calcium (II) complex wherein the calcium (II) ion content is $\geq$ 0.1 wt% relative to chitosan, and neither reference discloses chitosan formed of a gel of chitosan salt to which calcium (II) ions are bound, each and every limitation of the rejected claims is not taught by the references. Furthermore, because the references are dealing with different chitosan compositions (Goosen *et al.* discloses alginate-chitosan and alginate-poly-L-lysine-chitosan compound membranes and Struszczyk *et al.* discuss only microcrystalline chitosan), one of skill in the art would have no motivation to combine the cited reference or to modify one or the other to arrive at the claimed invention. Therefore, neither Goosen *et al.*(1990) nor Struszczyk *et al.* (1996) teach singly or in combination all elements of the claimed invention. At best, the Office has

engaged in inappropriate hindsight based on the Applicants' disclosure, which is improper (*see, e.g., MPEP* 2141) . Applicants respectfully request withdrawal of the rejection.

The Office has rejected claims 10-42 under 35 U.S.C. § 103(a) as being unpatentable over (Nies, 1995) in view of (Hashimoto *et al.*, 1995). Applicants respectfully traverse the rejection. The teachings of Nies (1995) combined with Hashimoto *et al.* (1995) fail to teach each and every limitation of the rejected claims. Nies fails to teach pH adjustments at all in the cited Abstract, and Hashimoto *et al.* (1995) also fails to disclose any pH-adjustment step, wherein the pH after chitosan molecular weight degradation is adjusted by adding an aqueous basic solution to the chitosan mixture to attain $4.0 \leq pH \leq 6.0$. Nies also fails to teach chitosan gels of any type at all.

The cited Abstract of Nies (1995) (the rest of the document is in German for which a translation was not provided) states: "The invention relates to a process for the preparation of aqueous solutions and gels of chitosan in which chitosan and an acidic chelating agent are dissolved in water. Such solutions can be drastically increased in viscosity or converted into highly viscous gels by adding salts of polyvalent metals and acids in which chitosan is only moderately soluble or is insoluble. From such solutions, salt-like chitosan/chelating agent adducts can be obtained by removing water or by precipitations using an organic solvent." Reference to adjusting the pH or digestion of chitosan in an acidic solution can not be found.

Hashimoto *et al.* (1995) simply teach that low molecular weight chitosan can be used to improved the solubility of poorly water-soluble drugs. At best, the reference notes that chitosan can be had from the degradation of chitin using enzymes or various reagents. Gel formation is not taught, much less any adjustment of the chitosan solution to obtain $4.0 \leq pH \leq 6.0$.

Neither reference teaches the claimed step of adjusting the pH of the chitosan molecular weight degradation step, wherein the solution attains $4.0 \leq pH \leq 6.0$. Hashimoto also fails to teach chitosan gels of any type at all. Therefore, each and every limitation of the rejected claims is not taught by the references, singly or in combination. Furthermore, one of skill in the art would have no motivation to combine the references or modify one in light of the other because Hashimoto *et al.* (1995) fails to teach chitosan gels at all. The rejections is respectfully requested to be withdrawn.

REFERENCES

Goosen, M., G. King, A. Daugulis, and P. Faulkner. 1990. MULTIPLE MEMBRANE MICROENCAPSULATION, US.

Hashimoto, M., M. Otagiri, and T. Imai. 1995. DRUG COMPOSITION, US.

Nies, B. 1995. PROCESS FOR PREPARING AQUEOUS CHITOSAN SOLUTIONS AND GELS, EP.

Struszczyk, H., and O. Kivekas. 1996. METHOD FOR SEED ENCRUSTING, US.

CONCLUSION AND REQUEST FOR RECONSIDERATION

Reconsideration and withdrawal of all claim rejections are respectfully requested. Applicants believe that the present application is in condition for allowance.

Should the Examiner have any questions or would like to discuss any matters in connection with the present application, the Examiner is invited to contact the undersigned at (312) 627-2126 or gzinkl@dykema.com.

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